Electronic submissions in the EU

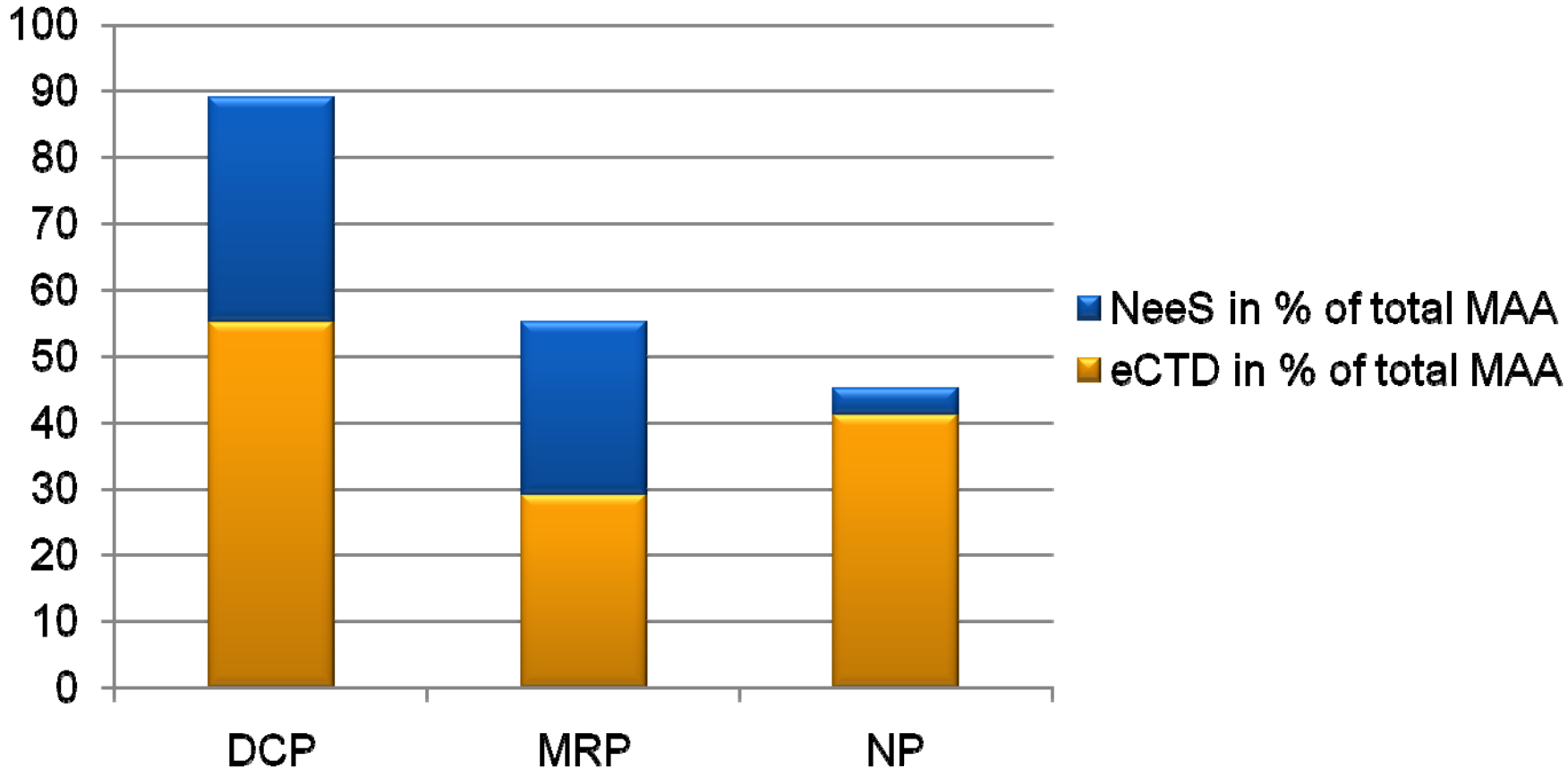
Karin Gröndahl

Head of Registration and Information Management

MPA, SWEDEN

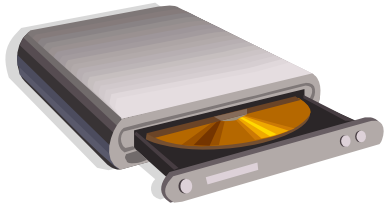
LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

New applications submitted to the MPA in e-only format (% of total MAA July - Dec 2010)



e-only in % of total applications: 222 in DCP, 58 in MRP, 27 in NP

Main problem in EU: Technical validation



- We have agreed and published validation criteria but different tools could anyway give different results
- The results could also be differently interpreted by different NCAs and different level of acceptance could apply
- The validation periods might be unnecessarily prolonged due to this and it takes a lot of resources both at industry and authorities
- Therefore, the TIGes Harmonisation group was given the responsibility to update the validation criteria for eCTD and NeeS to facilitate the validation

TIGes subgroup on harmonisation

A subgroup to TIGes (Telematics Implementation Group for electronic Submission)

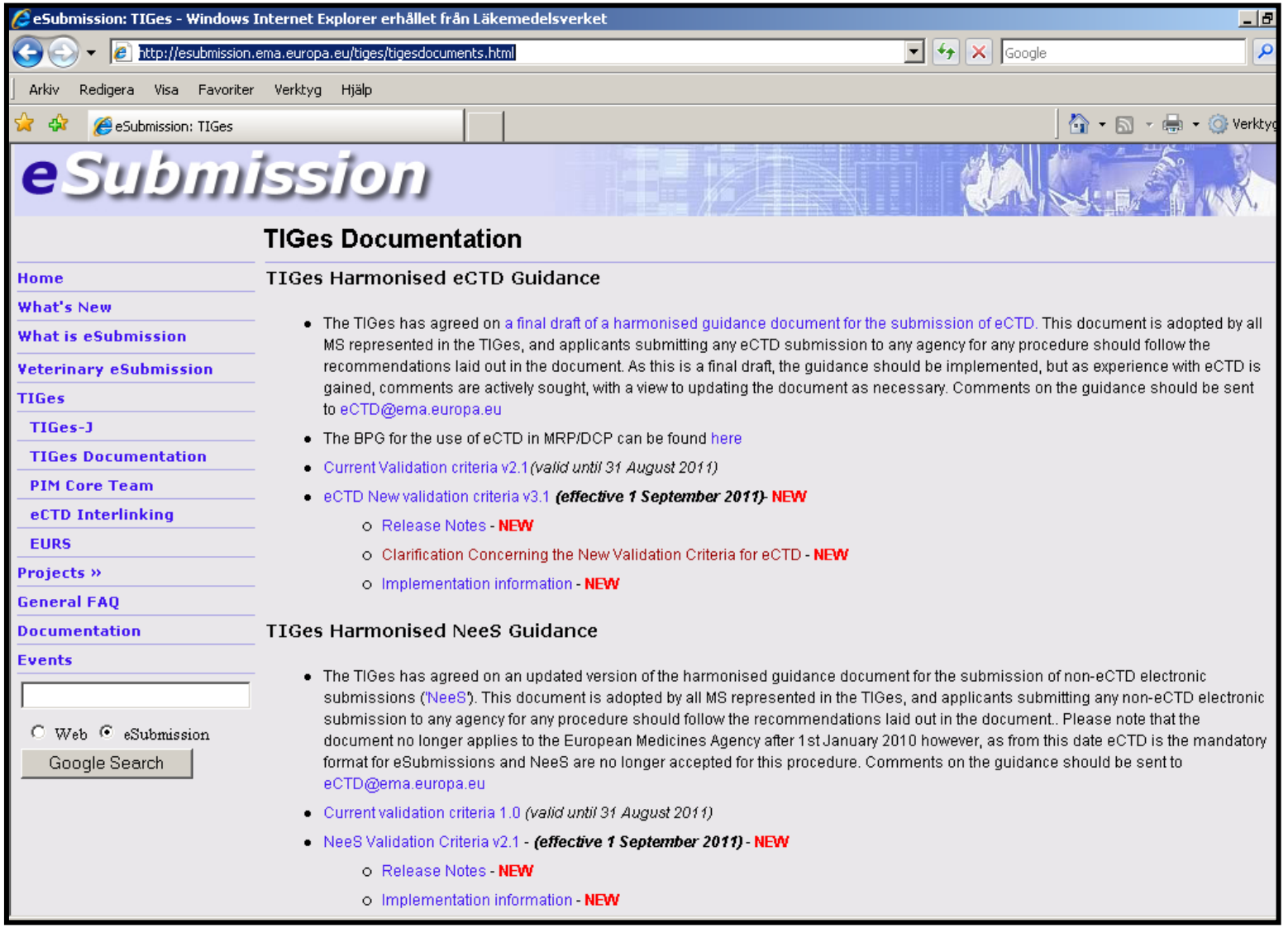
The objective of this group is the facilitation of electronic submissions in Europe through the publication of common guidance documents which should meet the needs of both industry and Competent Authorities.

Scope: eCTD and NeeS

New validation criteria for eCTD and NeeS

- **The aim was to write the criteria in a very clear way to prevent different interpretation by different validation tool vendors and also by different NCAs**
- **The new criteria were adopted by TIGes in January 2011**
- **They will come into force by 1 September, i.e. all NCAs should use them for submissions received from that day**

EMA eSubmission website



New validation criteria

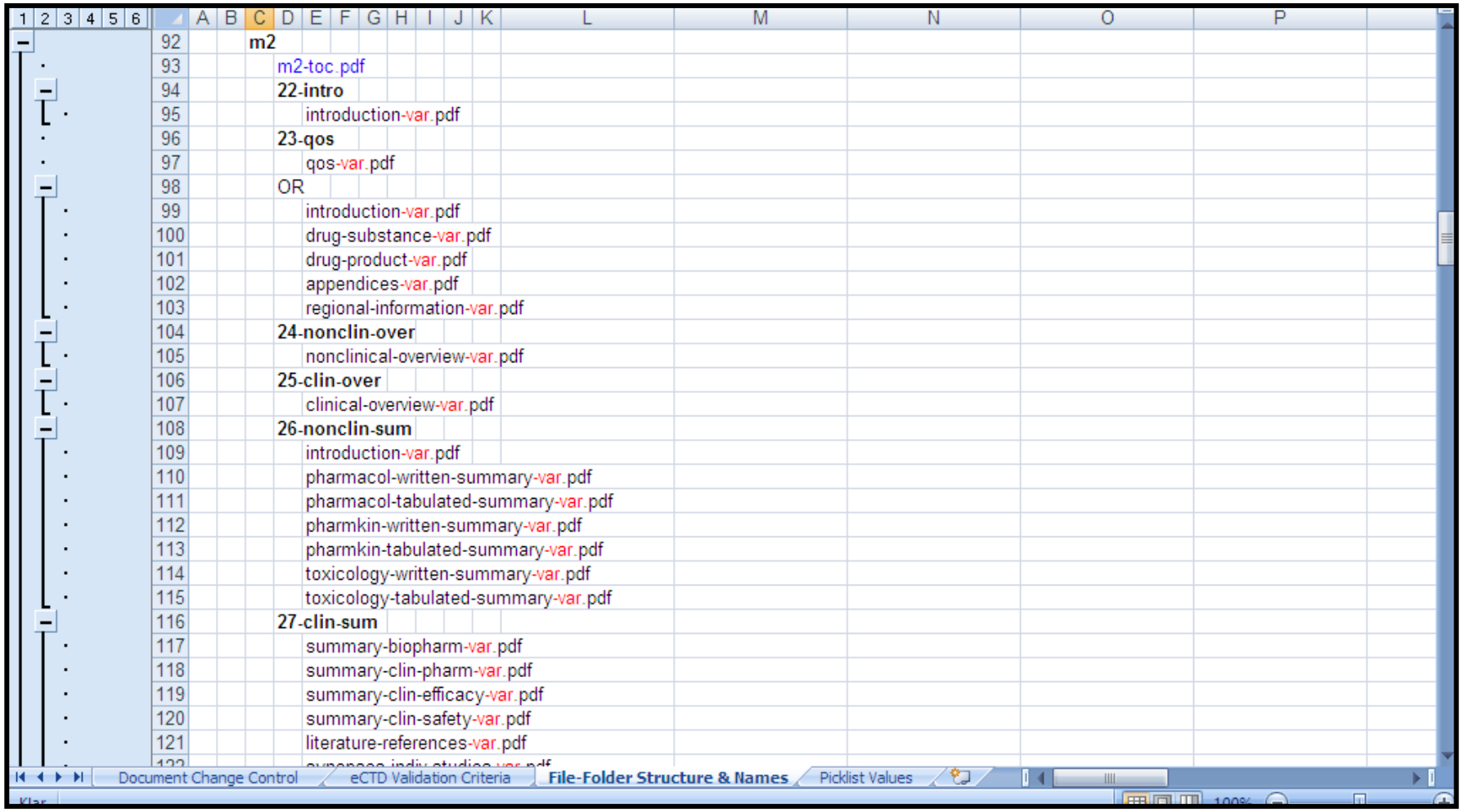
Number	Category	Validation Criterion	Type of check	Check can only be performed in context of other eCTDs in the lifecycle?	Comments
1,1	ICH DTD	The specified filename is used	P/F		File is named ich-ectd-3-2.dtd
1,2	ICH DTD	The correct placement is used	P/F		In the folder /XXXX/util/dtd
1,3	ICH DTD	A currently acceptable version of the DTD is used	P/F	Y	Currently acceptable with reference to any transition guidance (for example, not going back to an earlier version when a newer version has already been used for that eCTD)
1,4	ICH DTD	The valid version of the DTD is used (checksum matches the published value)	P/F		The checksum for v3.2 is 1d6f631cc6b6357f0f4fe378e5f79a27
2,1	ICH stylesheet	The specified filename is used	P/F		File is named ectd-2-0.xsl
2,2	ICH stylesheet	The correct placement is used	P/F		In the folder /XXXX/util/style
2,3	ICH stylesheet	A currently acceptable version of the stylesheet is used	P/F	Y	Currently acceptable with reference to any transition guidance (for example, not going back to an earlier version when a newer version has already been used for that eCTD)
2,4	ICH stylesheet	The valid version of the stylesheet is used (checksum matches the published value)	P/F		The checksum for v3.2 is 3a07a202455e954a2eb203c5bb443f77
3,1	EU M1 DTD	The specified filename is used	P/F		File is named eu-regional.dtd
3,2	EU M1 DTD	The correct placement is used	P/F		In the folder /XXXX/util/dtd
3,3	EU M1 DTD	A currently acceptable version of the DTD is used	P/F	Y	Currently acceptable with reference to any transition guidance (for example, not going back to an earlier version when a newer version has already been used for that eCTD)
3,4	EU M1 DTD	The valid version of the DTD is used (checksum matches the published value)	P/F		The checksum for v1.4 is 91654e96e3bafc5e89df7f892477b246
4,1	EU M1 leaf MOD file	The specified filename is used	P/F		File is named eu-leaf.mod
4,2	EU M1 leaf MOD file	The correct placement is used	P/F		In the folder /XXXX/util/dtd
4,3	EU M1 leaf MOD file	A currently acceptable version of the eu-leaf.mod file is used	P/F	Y	Currently acceptable with reference to any transition guidance (for example, not going back to an earlier version when a newer version has already been used for that eCTD)
4,4	EU M1 leaf MOD file	The valid version of the eu-leaf.mod file is used (checksum matches the published value)	P/F		The checksum for v1.4 is 2e976bc60658a964affa5026369a371e

New validation criteria

A	B	C	D	E	F
15,7	Files/Folders	Only valid characters are used in folder names	P/F		lower case characters a-z, digits 0-9 and hyphens are allowed (as documented in the ICH eCTD specification)
15,8	Files/Folders	There are no unreferenced files in M1, M2, M3, M4 and M5 folders	P/F		Including all subfolders within the m1-m5 folders but excluding 'util' folder and subfolders
15,9	Files/Folders	The only files in the sequence folder (/XXXX/…) are the index.xml and index-md5.txt	P/F		
15.10	Files/Folders	There are no empty folders	P/F		
15,11	Files/Folders	(If the procedure type in the envelope is "decentralised" or "mutual-recognition") The tracking table file is present in the correct location	P/F		The folder /XXXX/m1/eu/10-cover/common
15,12	Files/Folders	(If the procedure type in the envelope is "decentralised" or "mutual-recognition") The tracking table file is correctly	P/F		File is named common-cover-tracking.pdf or common-cover-tracking.xml
15.BP1	Files/Folders	Individual files do not exceed 100 MB in size	BP		Any deviation should always be reported by the validating tool. Files larger than 100 MB should be avoided. If there is a
15.BP2	Files/Folders	The recommended folder structure and folder names in the ICH and EU specifications are used	BP		Any deviation, including additional subfolders, should always be reported by the validating tool.
15.BP3	Files/Folders	The recommended file names from the ICH and EU specifications are used for all files	BP		Any deviation should always be reported by the validating tool. Note that the components of the file names in *italics* in Appendix 4 of the ICH eCTD specification are to be specified by the applicant (i.e. this is variable text). In EU Module 1 the variable (VAR) part of the file name can include hyphens. Note: a change request has been raised to allow hyphens in the Variable part of the file names Applicants using the eCTD for ASMF or for MAAs including an ASMF are reminded that the EU guidance recommends the use of "ap" and "rp" prefixes for content in the applicants part and restricted part, respectively. eCTD validation tools should accept these prefixes in Modules 1, 2 and 3. The CC code of the filename should not be checked against

Document Change Control | eCTD Validation Criteria | File-Folder Structure & Names | Picklist Values

New validation criteria



92	**m2**
93	m2-toc.pdf
94	**22-intro**
95	introduction-var.pdf
96	**23-qos**
97	qos-var.pdf
98	OR
99	introduction-var.pdf
100	drug-substance-var.pdf
101	drug-product-var.pdf
102	appendices-var.pdf
103	regional-information-var.pdf
104	**24-nonclin-over**
105	nonclinical-overview-var.pdf
106	**25-clin-over**
107	clinical-overview-var.pdf
108	**26-nonclin-sum**
109	introduction-var.pdf
110	pharmacol-written-summary-var.pdf
111	pharmacol-tabulated-summary-var.pdf
112	pharmkin-written-summary-var.pdf
113	pharmkin-tabulated-summary-var.pdf
114	toxicology-written-summary-var.pdf
115	toxicology-tabulated-summary-var.pdf
116	**27-clin-sum**
117	summary-biopharm-var.pdf
118	summary-clin-pharm-var.pdf
119	summary-clin-efficacy-var.pdf
120	summary-clin-safety-var.pdf
121	literature-references-var.pdf

Document Change Control | eCTD Validation Criteria | **File-Folder Structure & Names** | Picklist Values

What is new?

- ❑ **Each criterion checks for a single item**
- ❑ **eCTD and NeeS criteria are aligned in wording where relevant, i.e. when applicable for both formats**
- ❑ **Two levels of tests;**
  - **Pass / Fail** → ground for invalidation by authorities
  - **Best Practice** → should also be tested by applicant to facilitate for the assessment, but do not lead to invalidation

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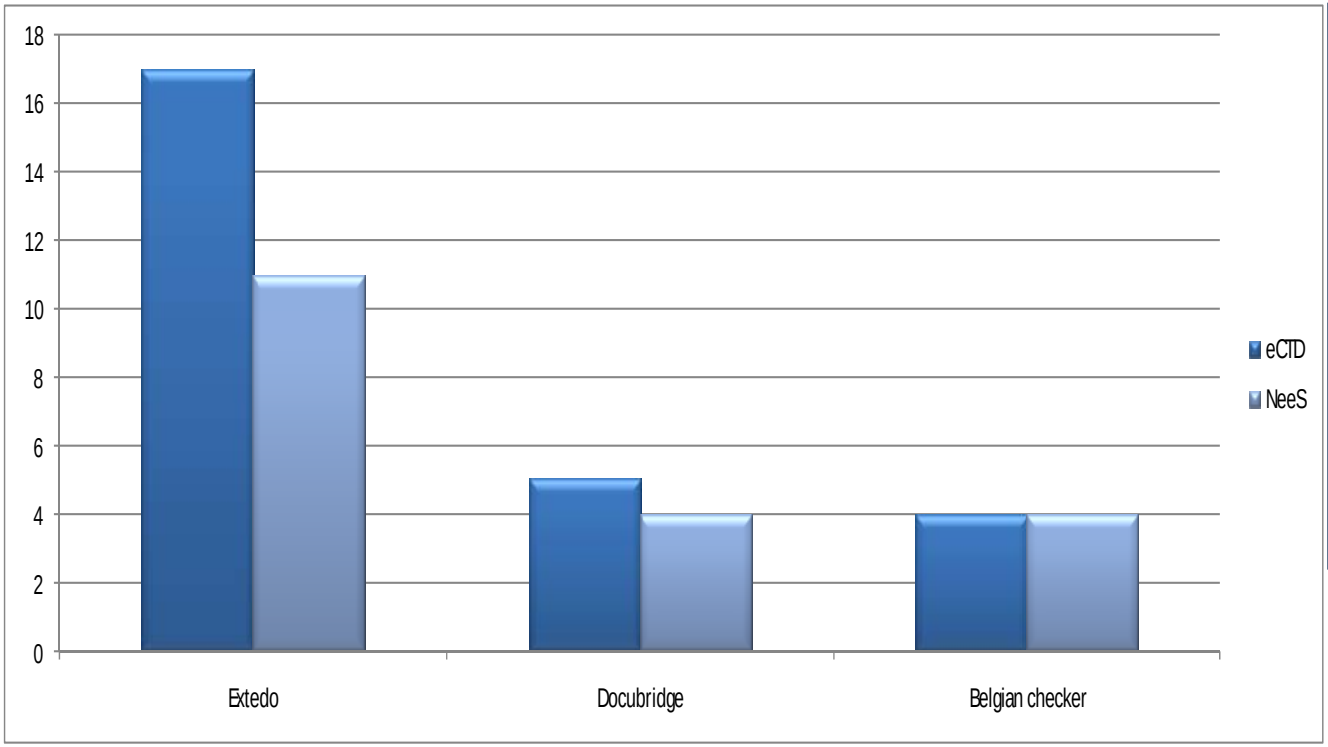
New validation criteria – please observe...

If it is not possible to perform the validation for a sequence in the presents of former submitted sequences (i.e. is done on the sequence in isolation), then the results of the tests for criteria marked with "Y" might not be reliable and this must be taken into account in the validation

(Now also clarified on the website.)

NCAs that had a validation tool for eCTDs Q3-4 2010
(from TIGes survey)



In total, 25 NCAs had a validation tool

15 of them rejected technically invalid applications

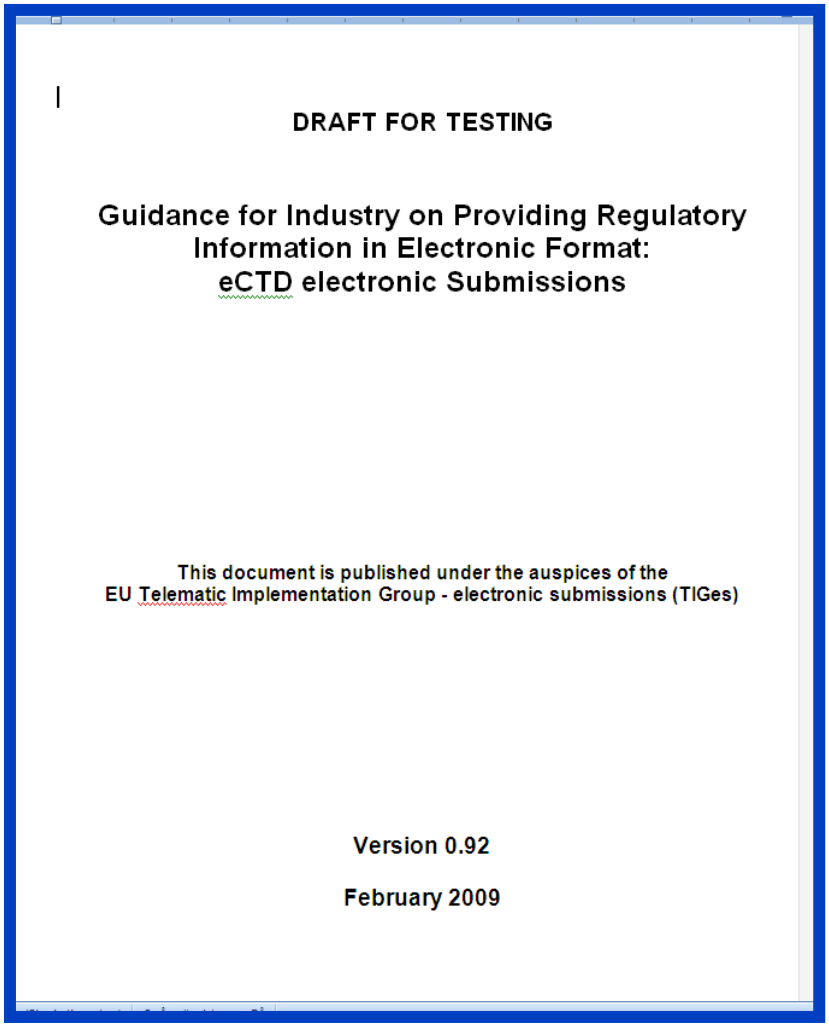
Technical validation process

The technical validation process will be further discussed by the authorities concerning:

- timelines for technical validation by authorities
- timelines for updates after technical invalidation
- the possibility of having a pre-step where RMS validates on behalf of all CMS within the MRP/DCP in the future

A validation training/workshop will be organised by members in the Harmonisation group in August for all MSs to learn and to harmonise the technical validation

EU eCTD Guidance



DRAFT FOR TESTING

Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions

This document is published under the auspices of the EU Telematic Implementation Group - electronic submissions (TIGes)

Version 0.92

February 2009

First version published in 2009 at the EMA eSubmission website http://esubmission.ema.europa.eu/tiges/tigesdocuments.htm

To be updated before September 2011

Change Requests for the guidance should be sent in accordance with the TIGes published CR procedure

eCTD EU guidance – major changes in next version

- **All new things introduced with the new validation criteria are included in the guidance, except where the EU M1 eCTD specification is concerned.**

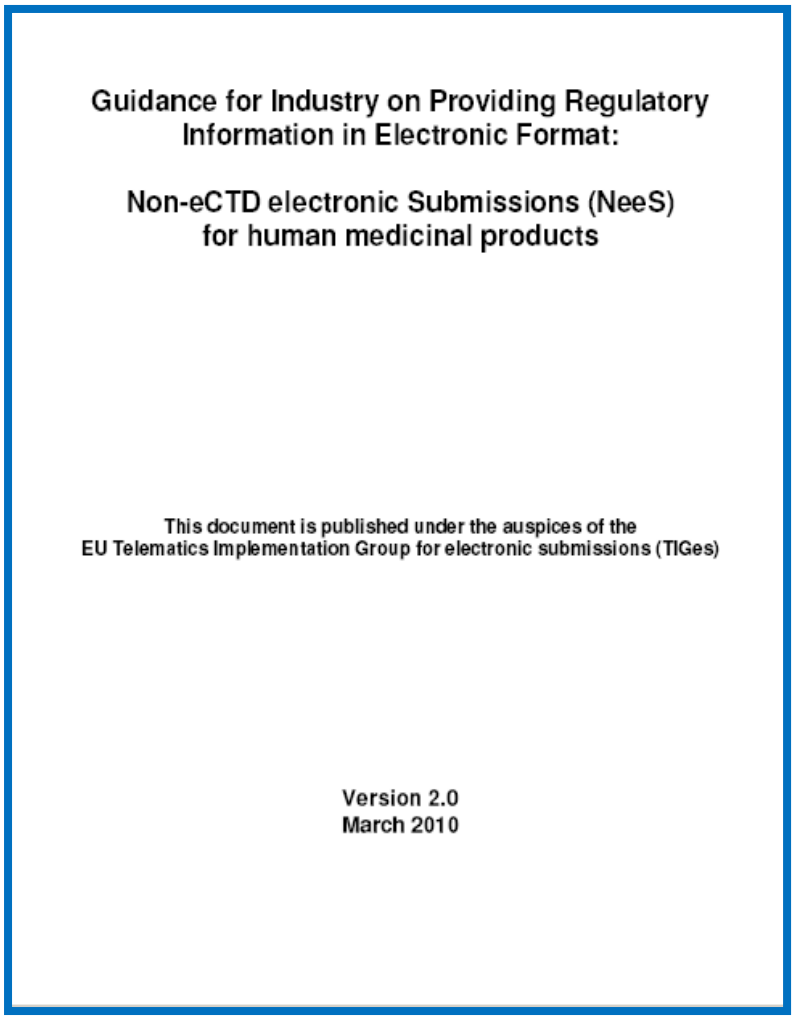
  (*The specification will be updated by TIGes Interlinking/EMA)*

- **Things from published Q&As have been incorporated.**
- **RTF, ZIP/TGZ not to be acceptable in EU eCTD**
- **Clarification on use of Related sequences**
- **Clarification on translations to be provided outside the eCTD (in a separate folder) also when requested at the time of submission of a variation type IA or IB**

eCTD EU guidance document – major changes

- Guidance of changing from NeeS or paper to eCTD
- Guidance on different kind of Baselines, also "re-baselining" when really needed
- File/folder naming - reference to the validation criteria
- Clarification on PDF version requirements
- Introducing a *recommendation* for a Tracking table also for CP and NP
- Clarified that "old", earlier submitted, sequences should not be again validated in a new MRP or a RUP

EU NeeS Guidance


Guidance for Industry on Providing Regulatory Information in Electronic Format:

Non-eCTD electronic Submissions (NeeS) for human medicinal products

This document is published under the auspices of the EU Telematics Implementation Group for electronic submissions (TIGes)

Version 2.0
March 2010

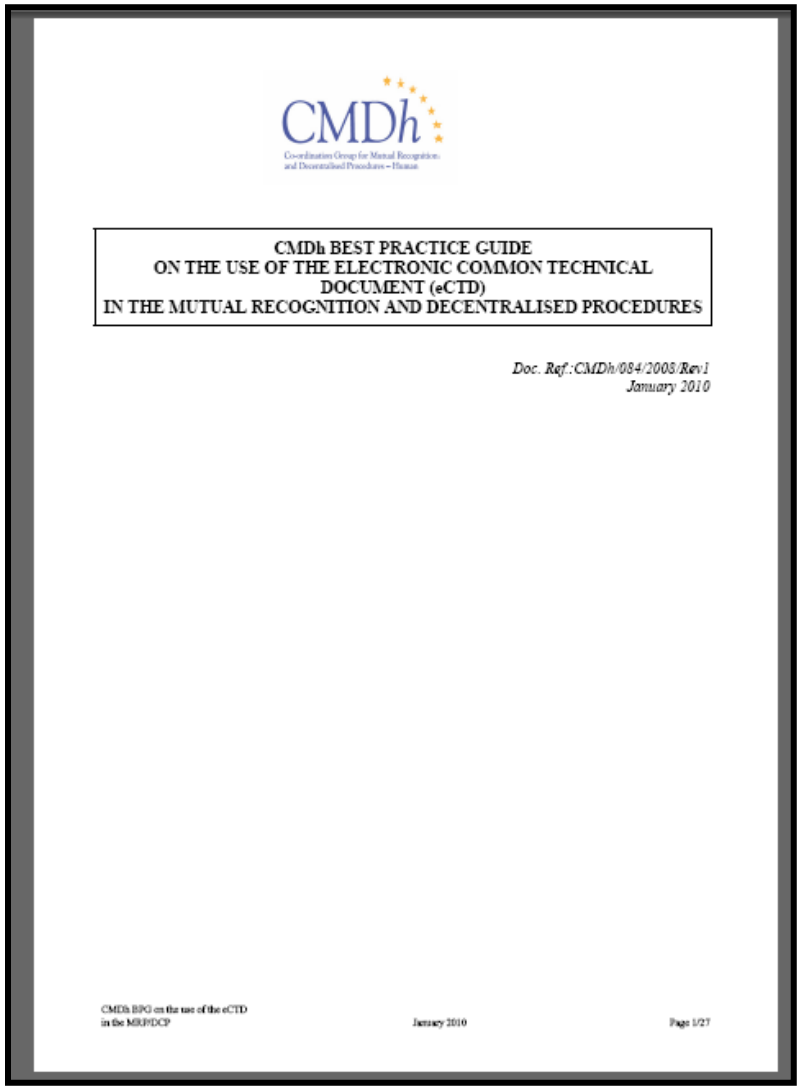
First version published 2008 at the EMA eSubmission website http://esubmission.ema.europa.eu/tiges/tigesdocuments.html

To be updated before September 2011

Change Requests for the guidance should be sent in accordance with the TIGes published CR procedure

NCA's eSubmission requirements

BPG for eCTD in MRP/DCP



CMDh

Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

CMDh BEST PRACTICE GUIDE ON THE USE OF THE ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD) IN THE MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES

Doc. Ref.: CMDh/084/2008/Rev1
January 2010

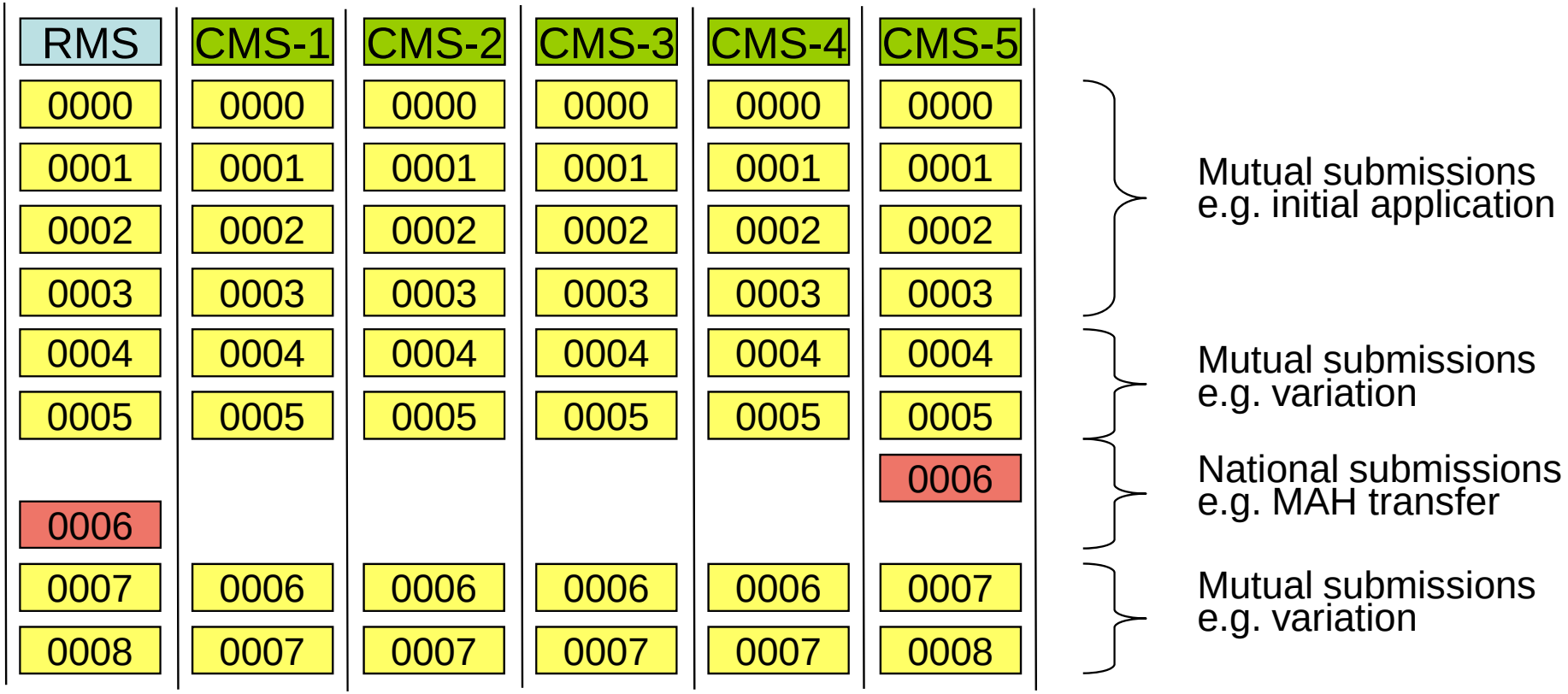
CMDh BPG on the use of the eCTD in the MRP/DCP — January 2010 — Page 1/27

First version published in 2008 at the CMDh eSubmission website http://www.hma.eu/277.html

To be updated before September 2011

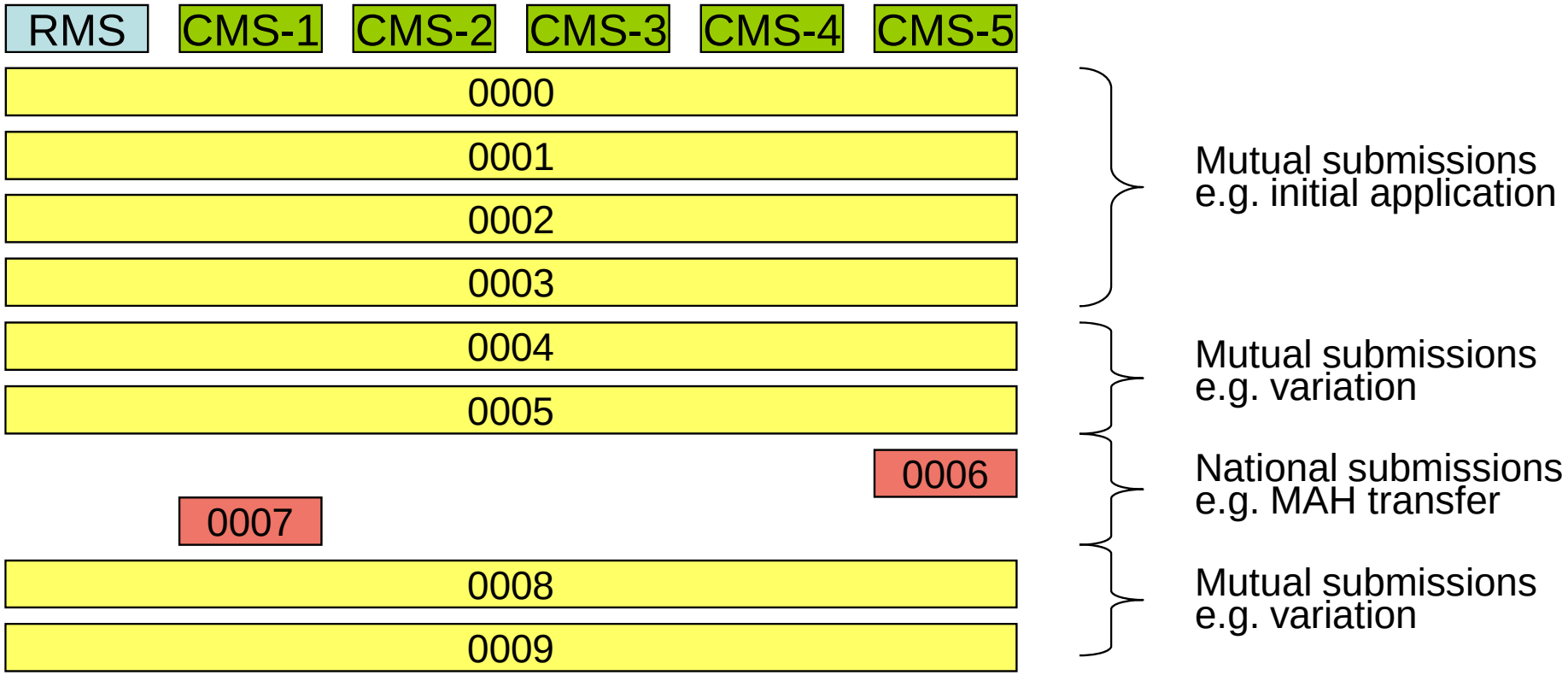
Change Requests for the guidance could be sent in accordance with the TIGes published CR procedure

Parallel National model



This model is only acceptable until 31 December 2011

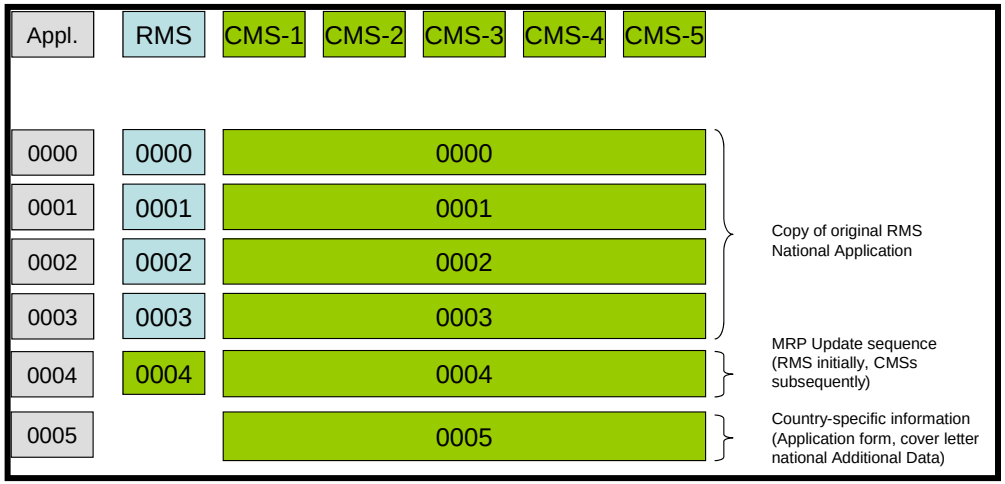
Comprehensive model

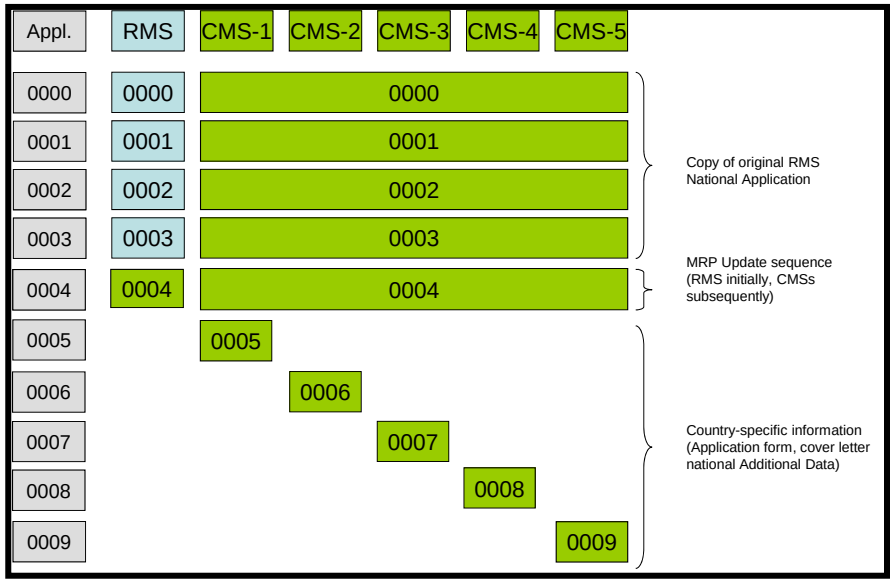


Start of MRP

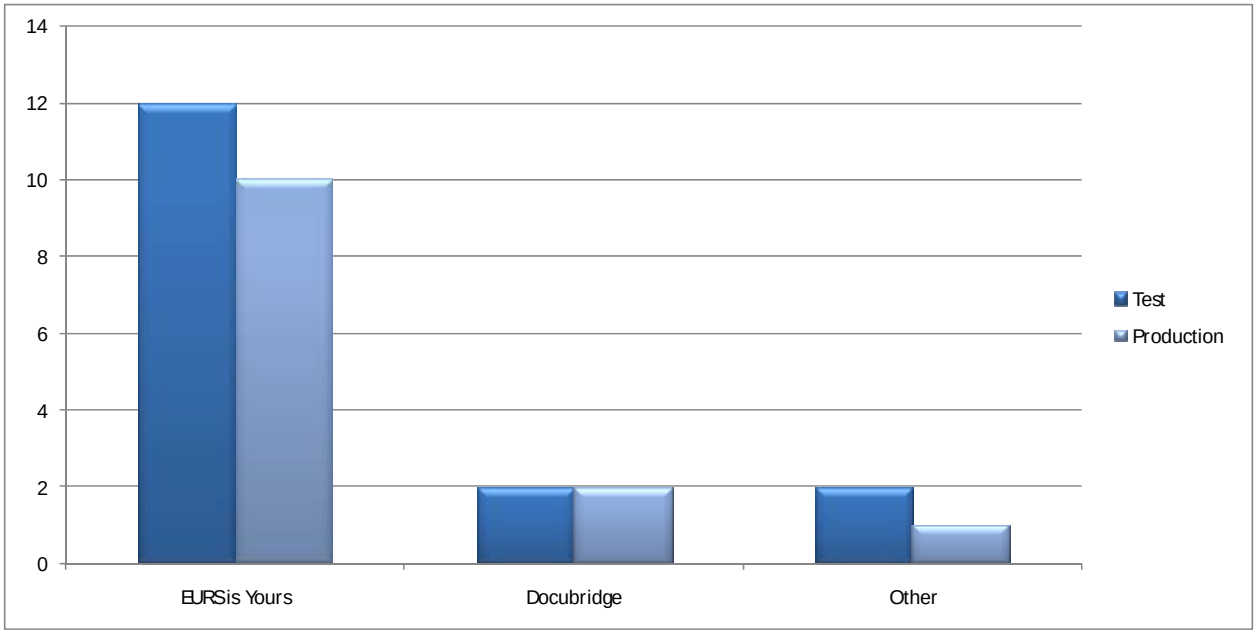
Appl.	RMS	
0000	0000	Initial MAA
0001	0001	Validation Update
0002	0002	Response to Questions
0003	0003	Final agreed National Product Information

National Approval





NCAs having a review tool for eCTDs Q1-2 2009
(from TIGes survey)

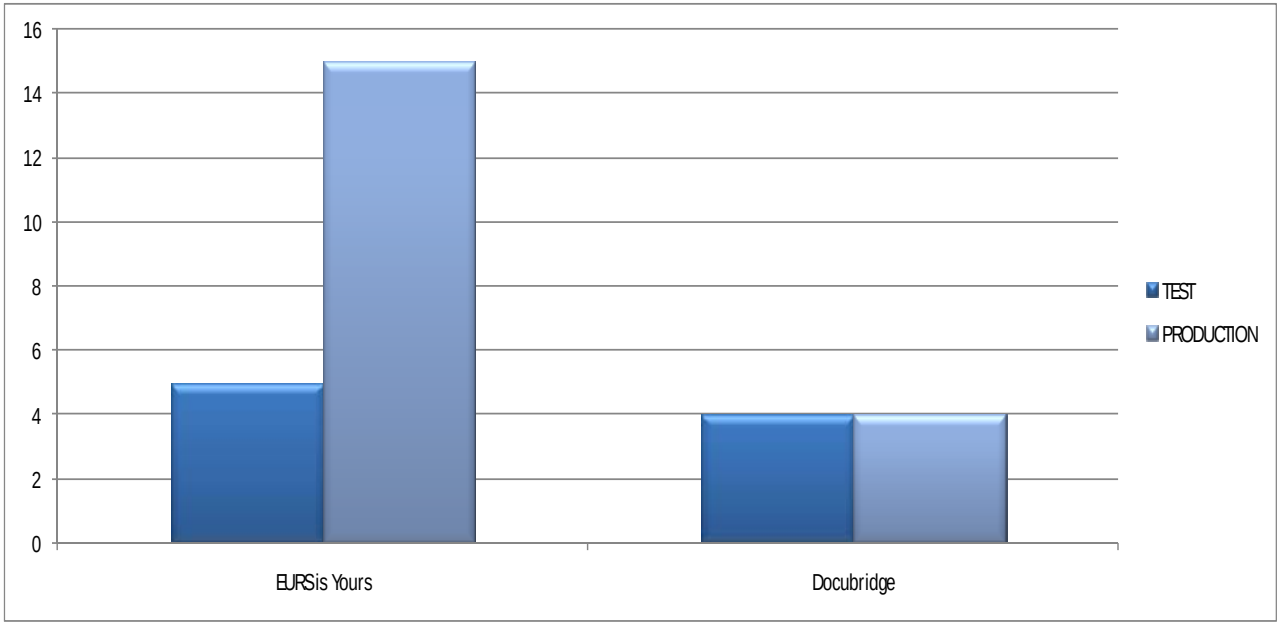


13 NCAs had a review tool in production and 16 had it in test

So, all EU MSs could not fully benefit from eCTDs

NCAs having a review tool for eCTDs Q3-4 2010

(from TIGes survey)

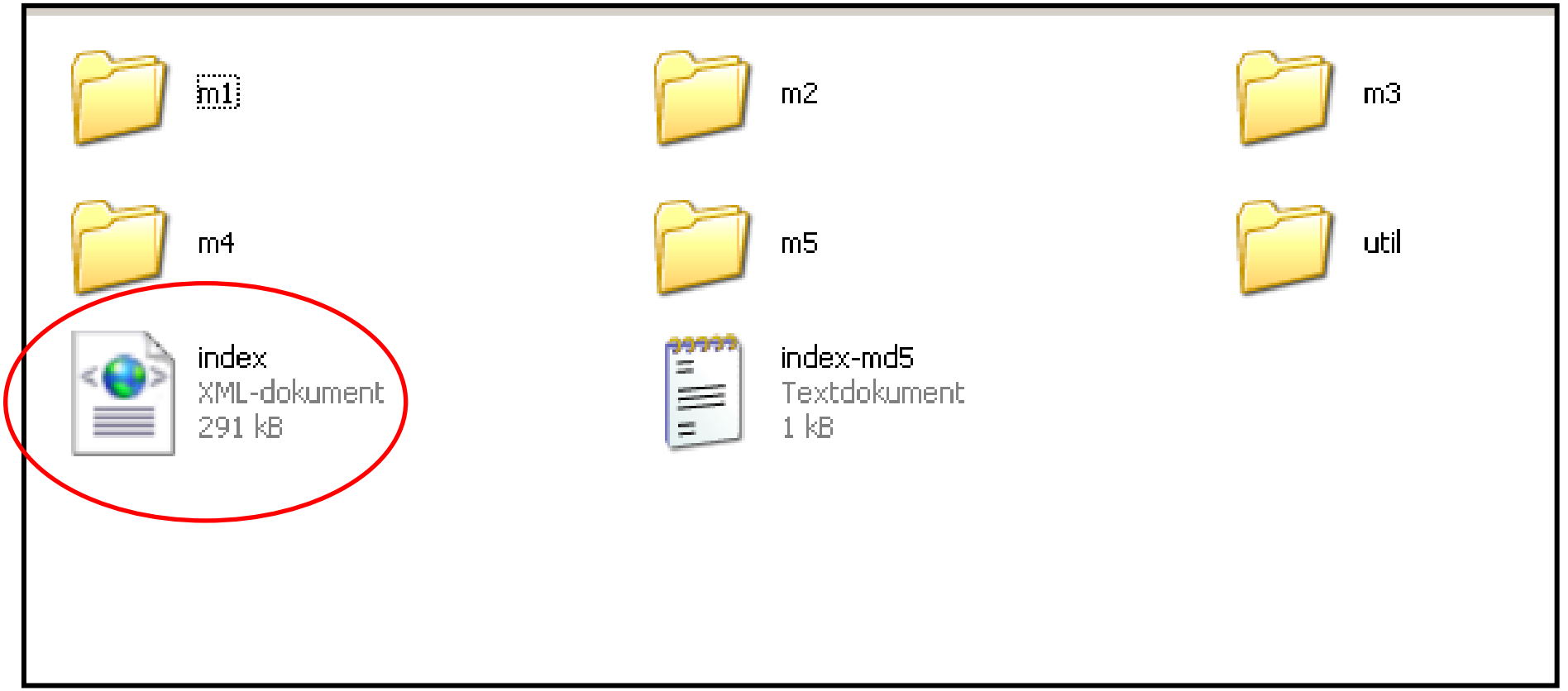


In total, 24 NCAs had a review tool

19 of them had it in production

So, still all EU MSs cannot fully benefit from eCTDs

If there is no review tool – how to use the eCTD?



eCTD DTD version 3.2

- m1-administrative-information-and-prescribing-information
  - eu-regional.xml [new]

EU Module 1

DTD version 1.4

Envelope for UK

Submission:	Type: Variation Type IA Mode: Grouping Number: IT/H/[redacted]
Tracking Number(s):	IT/H/[redacted] IT/H/ IT/H/
Applicant:	[redacted]
Agency:	Medicines and Healthcare products Regulatory Agency, Market Towers (UK-MHRA)
Procedure:	Mutual Recognition Procedure (MRP)
Invented Name:	[redacted]
INN:	
Sequence:	0006
Related Sequence:	0000
Submission Description:	Mutual Recognition variation

Envelope for SE

Submission:	Type: Variation Type IA Mode: Grouping Number: [redacted]
Tracking Number(s):	IT/H/[redacted] IT/H/ IT/H/
Applicant:	[redacted]
Agency:	Sweden - Medical Products Agency (SE-MPA)
Procedure:	Mutual Recognition Procedure (MRP)
Invented Name:	[redacted]
INN:	
Sequence:	0006
Related Sequence:	0000
Submission Description:	Mutual Recognition variation

scroll

scroll

1.0 Cover Letter

For BE:
- Cover letter May 11 (new)

For DK:
- Cover letter May 11 (new)

For FR:
- Cover letter May 11 (new)

For DE:
- Cover letter May 11 (new)

For IE:
- Cover letter May 11 (new)

For IT:
- Cover letter May 11 (new)

For LU:
- Cover letter May 11 (new)

For NL:
- Cover letter May 11 (new)

For PT:
- Cover letter May 11 (new)

For ES:
- Cover letter May 11 (new)

For SE:
- Cover letter May 11 (new)

For UK:
- Cover letter May 11 (new)

For COMMON:
- Tracking Table May 2011 (new)

1.2 Application Form

For COMMON:
- English application form variation [redacted] (new)
- Annex 1 ? Letter of authorisation for communication on behalf of the applicant - [redacted] (new)

For ES:
- Spanish application form grouped variation [redacted] (new)

1.3 Product Information

1.3.1 SPC, Labelling and Package Leaflet

1.3.2 Mock-up

SEQUENCE [redacted] BLE

	CMSs						
LU	BE	NL	FR	DE	IE	PT	
Dec09	Dec09	Dec09	Dec09	Dec09	Dec09	Dec09	Dec
June10	June10	June10	June10	June10	June10	June10	June
Aug10	Aug10	Aug10	Aug10	Aug10	Aug10	Aug10	
Dec10	Dec10	Dec10	Dec10	Dec10	Dec10	Dec10	
Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	Apr 11	
-	-	-	-	-	-	-	
May 11	May 11	May 11	May 11	May 11	May 11	May 11	

- m1-administrative-information-and-prescribing-information
  - eu-regional [new]

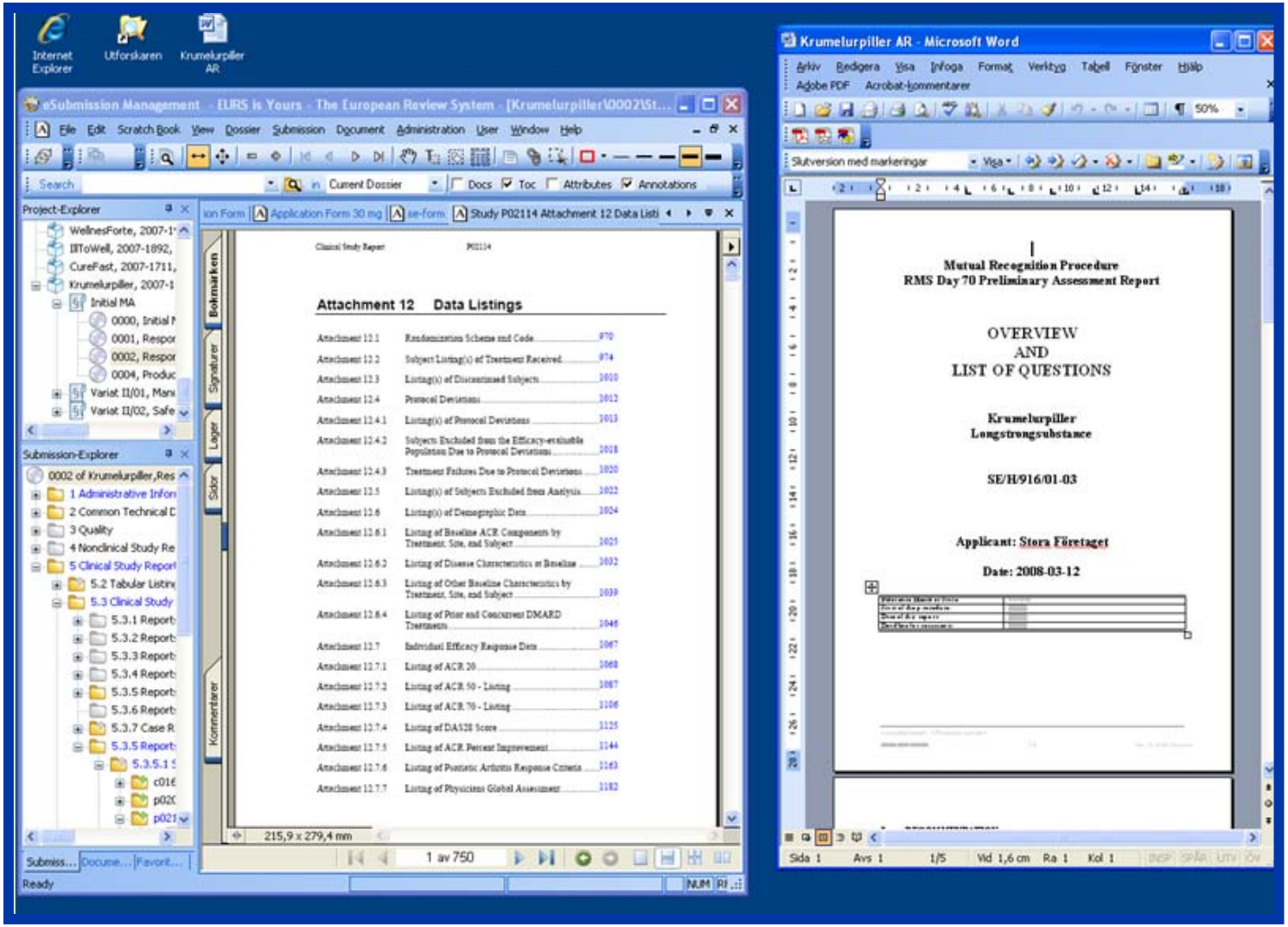
- m2-common-technical-document-summaries
  - m2-3-quality-overall-summary
    - m2-3-introduction
      - Introduction [new]
    - m2-3-s-drug-substance [manufacturer: [redacted]
      - General Information [new]
      - Manufacture [new]
      - Characterisation [new]
      - Control of Drug Substance [new]
      - Reference Standards or Materials [new]
      - Container Closure System [new]
      - Stability [new]
    - m2-3-p-drug-product [manufacturer: [redacted]
      - Description and Composition of the Drug Product [new]
      - Pharmaceutical Development [new]
      - Manufactures [new]
      - Control of Excipients [new]
      - Control of Drug Product [new]
      - Reference Standards or Materials [new]

However, the index file lists all documentation as if it is there, even if it is physically provided in an earlier sequence.

If you use this sequence in isolation, you can't access the file here, but you get a hint where it is.

    - m3-2-s-1-general-information
      - m3-2-s-1-1-nomenclature
        - Nomenclature - [redacted]
        - Nomenclature -
        - Nomenclature -
      - m3-2-s-1-2-structure
        - Structure - [redacted]
        - Structure -
        - Structure -

Use of a Review system



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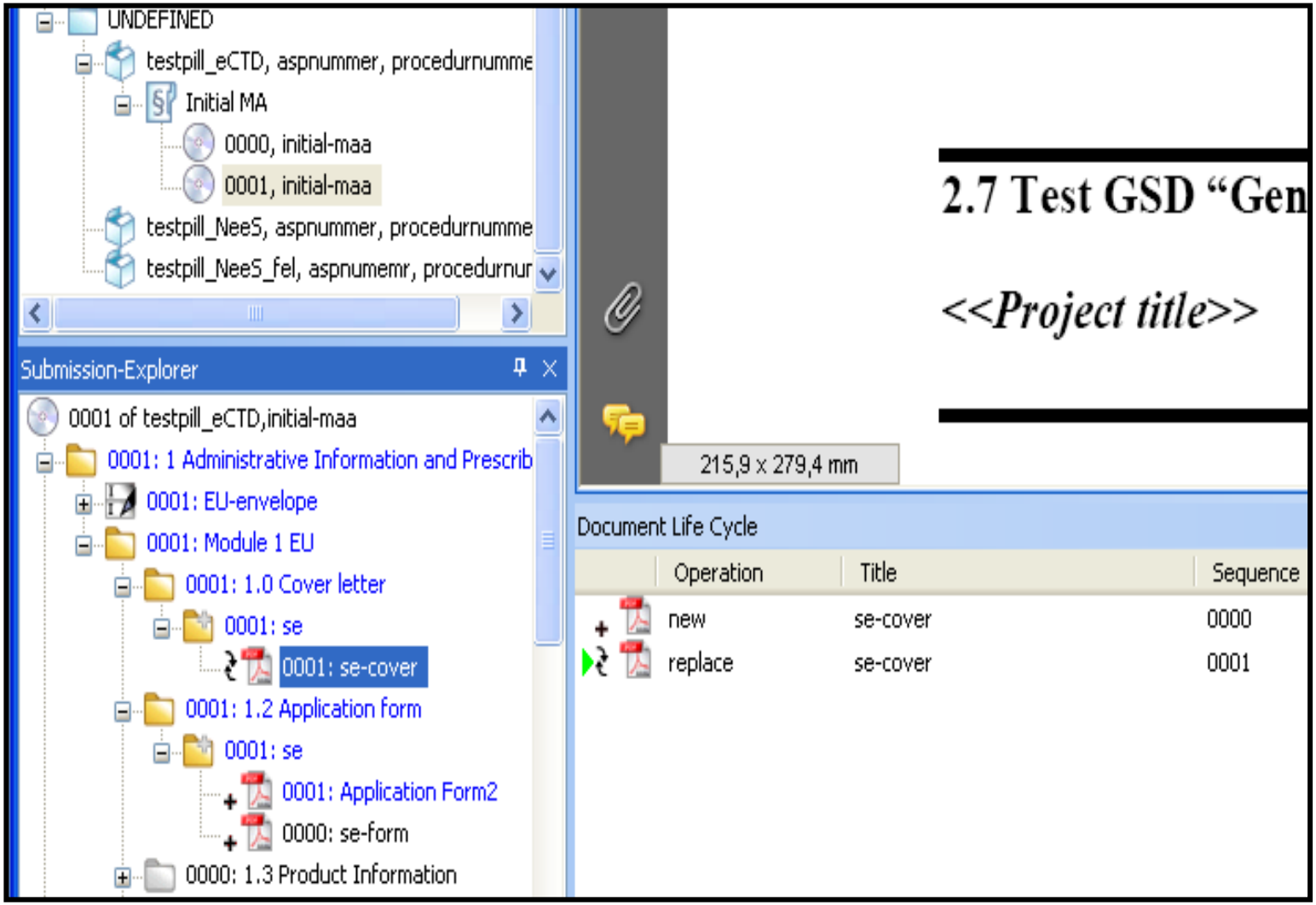

Thank you for your attention!

Karin Gröndahl
karin.grondahl@mpa.se

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY